21 CFR Part 101

[Docket No. 91N-0102]

RIN 0905-AD08

Food Labeling: Health Claims; Zinc and Immune Function in the Elderly

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing not to authorize the use on foods, including dietary supplements, of health claims relating to the association between zinc and immune function in the elderly. FDA has reviewed the scientific data in conformity with the requirements of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) and has tentatively concluded that there is not a sufficient basis to support the use of health claims relating to this topic. The agency's examination of publicly available evidence revealed that a specific protective role of zinc supplementation of the elderly population has not been demonstrated. Although some small clinical studies suggested such a relationship, these results were not substantiated in subsequent research using better study designs and larger samples.

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the Nutrition Labeling and Education Act of 1990.

FOR FURTHER INFORMATION CONTACT: James E. Hoadley, Center for Food Safety and Applied Nutrition (HFF-268), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5104.

SUPPLEMENTARY INFORMATION:

I. Background

A. Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the 1990 amendments (Pub. L. 101-535), which amend the Federal Food, Drug, and Cosmetic Act (the act). Section 403(r) of the act (21 U.S.C. 343(r)) authorizes the Secretary of Health and Human Services and FDA by delegation to issue regulations authorizing nutrient content and health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under the act (21 U.S.C. 343(r)(1)(B)).

Published elsewhere in this Federal Register is a proposed rule to establish general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs, or other nutritional substances (referred to generally as "substances") to a disease or health-related condition on food labels and in labeling for conventional foods and dietary supplements. In this companion document, FDA has tentatively determined that such claims would only be justified for substances in dietary supplements as well as in conventional foods if it determines, based on its review of all the publicly available scientific evidence (including evidence from well designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (sections 3(b)(1)(A)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x)) that within 12 months of enactment, the Secretary of Health and Human Services shall issue proposed regulations to implement section 403(r) of the act and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including zinc and immune function in the elderly, meet the requirements of the act.

In this document, the agency will consider whether a label or labeling claim on a food, including conventional foods and dietary supplements, on the relationship between zinc and immune function in the elderly would be justified under the standard proposed in the companion document entitled "Food Labeling: General Requirements for Health Claims for Food.

B. Zinc and Immune Function in the Elderly: Public Health Aspects

1. Zinc and Immune Function

Immune function refers to the body's defense processes to prevent and contain infection. The immune system is composed of lymphoid, thymus, and bone marrow cells. Poor nutrition (for example, malnutrition consisting of inadequate protein and calorie intake and multiple nutrient deficiencies) increases susceptibility to infectious disease (Refs. 1 through 4). In addition, diminished immune function is recognized as an adverse consequence of deficiencies of several specific nutrients including iron, zinc, copper, magnesium, selenium, vitamin E, vitamin C, vitamin B_6, vitamin B_{12}, and folic acid. The effect that a deficiency in a particular nutrient has on immune function in human populations is not well understood. Zinc deficiency and immune function have been investigated extensively because studies in humans and animals have shown that zinc deficiency causes a selective suppression of lymphoid organ weight and abnormalities in immune responses.

Experiments in zinc-deficient animals and humans have shown that zinc is essential for specific immune function (Refs. 5 through 8). Immunological disorders of some disease conditions characterized by secondary zinc deficiencies can be corrected by zinc supplementation (Refs. 5 and 7). Such disease states and conditions include acrodermatitis enteropathica, alcoholism, diabetes, gastrointestinal disorders, sickle cell anemia, some cancers, protein-calorie malnutrition, parenteral nutrition with inadequate zinc, and hypoglobulinemia. There is no evidence, however, that immune function in healthy persons can be enhanced by zinc supplementation.

Zinc is considered to be relatively nontoxic, particularly if taken orally. However, adverse effects, which include impaired immune function, are known to occur with zinc intake in excess of the Recommended Dietary Allowance (RDA) (Ref. 9).

2. Mechanisms and Measures of Immune Function

The immunologic defense mechanisms mediated by T lymphocytes are collectively known as "cell-mediated immunity." T. lymphocytes, a specific type of white blood cell, attack and kill cells infected with viruses, bacteria, and protozoa. Thymic hormone stimulates maturation and differentiation of immature lymphocytes into several specific types of functional T lymphocytes. Thymic hormone requires zinc for activation. Various subsets of differentiated T lymphocytes (e.g., "helper", "suppressor", and "killer" T cells) can attach to infected cells and kill them directly or can function indirectly by releasing substances that influence the actions of other immune cells.

Several common tests are used to measure the level of cell-mediated

immune function. In the delayed cutaneous hypersensitivity (DCH) test, a small amount of foreign substance (an antigen) is injected under the skin. With normal functioning cell-mediated immunity, a localized inflammatory reaction develops at the site of the injection within 48 hours. The immune response to the antigen is measured by the diameter of the welt and inflammation appearing at the site. "Anergy" is a term used to describe the condition in which no cell-mediated allergic reaction occurs in response to such antigen injection.

Another type of test of cell-mediated immunity uses lymphocytes separated from blood samples and cultured in test tubes. Addition of a small amount of mitogen (a substance such as bacterial fragments) to the isolated lymphocytes stimulates functional, immunocompetent T lymphocytes to divide and proliferate. Impaired cell-mediated immunity is indicated by a failure of the mitogen to stimulate T lymphocyte proliferation. The lymphocyte proliferative response (LPR) is a measure of the rate of lymphocyte division in response to a mitogen challenge.

Zinc deficiency has been associated with decreased thymic hormone levels and with a corresponding decrease of both functional T lymphocytes and cell-mediated immunity in experimental animals and humans, as shown by anergy in DCH and decreased LPR (Refs. 8 and 10).

3. Immune Function in Aging

One of the physiologic changes that characterizes aging is a gradual senescence of some components of the immune system, particularly cell-mediated immune function (Refs. 5, 11, and 12). The primary age related changes in immune systems of both human and experimental animals result from gradual thymic atrophy and changes in the T lymphocyte population. There are age related decreases in the number of blood T lymphocytes as well as in the proportion of helper/inducer T lymphocytes and increases in the proportion of immature T lymphocytes. Accompanying the change in T cell population is a functional decline in cell-mediated immunity as indicated by reduced lymphocyte proliferation in response to mitogens.

Progressive impairment of cellular immunity observed in generalized malnutrition, including zinc deficient states, is similar in some respects to the age related decline of cell-mediated immune function. When insufficient protein calorie nutrition is responsible for depressed immune function, improved diet may restore such function and improve disease resistance. There is evidence that a balanced, complete nutritional supplementation can improve impaired cell-mediated immunity in protein-calorie malnourished elderly (Ref. 13).

4. Zinc Nutritional Status of the Elderly in the United States

Several reports have suggested that the elderly U.S. population may be at risk of zinc deficiency. A review of reports by 17 different groups concerning zinc intake in the elderly has recently been published (Ref. 14). The results of dietary surveys have been fairly consistent in suggesting that elderly persons consume zinc at less than RDA levels. Diets representative of those consumed by elderly women generally contain less dietary zinc than do those for elderly men (Ref. 15), and institutionalized subjects generally consume less zinc than do persons living at home (Refs. 16 and 17).

Intake of zinc appears to diminish as elderly persons advance in age (Refs. 14 and 18). Small studies of selected populations have also identified pockets of zinc insufficiency in some populations (Ref. 14). Additionally, the elderly frequently alter their dietary habits and may also lose their appetites and reduce their food intake (i.e., become anoretic).

For these reasons, the elderly population has been proposed as one of the groups which may have a high incidence of inadequate zinc nutriture (Refs. 19 through 21). The question of adequacy of zinc nutriture in the elderly is one of the issues that FDA examined in this review.

C. Zinc: Regulatory History

One zinc salt, zinc methionine sulfate, is regulated as a direct food additive for use as a special dietary and nutrient food additive in 21 CFR 172.399.

Five other zinc salts are listed in part 182 (21 CFR part 182) as generally recognized as safe (GRAS) for use in dietary supplements or as nutrients: Zinc chloride (§§ 182.5985 and 182.8985), zinc gluconate (§§ 182.5988 and 182.8988), zinc oxide (§§ 182.5991 and 182.8991), zinc stearate (§§ 182.5994 and 182.8994), and zinc sulfate (§§ 182.5997 and 182.8997). No zinc compounds are affirmed as GRAS in part 184—Direct Food Substances Affirmed as Generally Recognized as Safe (21 CFR part 184) nor under part 186—Indirect Food Substances Affirmed as Generally Recognized as Safe (21 CFR part 186). FDA proposed to affirm the GRAS status of the use of zinc salts in a document published on October 26, 1982 (47 FR 47441). FDA proposed to affirm as GRAS the use of zinc oxide and zinc sulfate as direct food ingredients, to affirm as GRAS the use of zinc chloride as an indirect food ingredient, and to remove zinc chloride and zinc stearate from the listing in part 182 (§§ 182.8985 and 182.8994). For technical reasons not related to the safety of the compounds,

FDA proposed on August 28, 1991 (56 FR 42668) to withdraw pre-1986 GRAS proposals, one of which is the use of zinc salts.

FDA has issued a health fraud bulletin pertaining to drug products, including vitamins and minerals, that bear claims that they enhance, strengthen, or otherwise benefit the immune system for the purpose of preventing or treating any disease condition. The bulletin stated that such products are drugs under section 201(g)(1)(B) of the act (21 U.S.C. 321(g)(1)(B) (FDA Health Fraud Bulletin No. 11. *Immune System Products,* August 17, 1987).

D. Evidence Considered in Reaching the Decision

FDA has reviewed all relevant scientific evidence on zinc and immune function in the elderly. The scientific evidence reviewed by FDA included all relevant studies considered in two U.S. Government documents: "The Surgeon General's Report on Nutrition and Health," U.S. Department of Health and Human Services, 1988 (Ref. 22) (the Surgeon General's report) and the U.S. Department of Agriculture (USDA) and DHHS pamphlet "Nutrition and Your Health, Dietary Guidelines for Americans" (Ref. 23). FDA reviewed relevant studies considered in three nongovernment documents: the National Research Council's report "Diet and Health: Implications for Reducing Chronic Disease Risk," National Academy of Sciences (Ref. 24), the Tenth Edition of "Recommended Dietary Allowances" (Ref. 25) and the Life Sciences Research Office of the Federation of American Societies of Experimental Biology report "Zinc and Immune Function in the Elderly" (Ref. 26) (the Life Science Research Office report). FDA updated the conclusions reached in these documents by reviewing all human studies and all review articles relevant to the topics that were published in the literature since the publication of these documents.

To assure that its review of relevant evidence was complete, FDA requested, in the Federal Register of March 28, 1991, (56 FR 12932) scientific data and information on the 10 specific topic areas identified in section 3(b)(1)(A) of the 1990 amendments. The topic of zinc and immune function in the elderly was

among the 10 subjects on which the agency requested information.

E. Comments Received in Response to FDA Request for Scientific Data and Information

In response to the March 28, 1991 notice in the **Federal Register**, FDA received six comments from food manufacturers or processors, trade associations of dietary supplement manufacturers, national associations of public health and nutrition officials, and the Government of Canada. The comments dealt with the issue of zinc and immune function in the elderly as well as with the goals and requirements of the 1990 amendments. One comment was from a private citizen, who submitted a computer search of medical literature. FDA reviewed all of the documents, including letters, press releases, scientific articles, review articles, and recommendations included in submissions that it received. The data submitted in scientific articles were included in FDA's review of the scientific literature.

Comments from a food manufacturer and from a trade association of nutrient supplement manufacturers included a recommendation that FDA include additional population groups and additional nutrients in its evaluation of nutrition/immune function relationships for label health claims. Another comment noted that dietary intake data from several sources indicate that the zinc intake of several age groups is less than the RDA. One comment noted that although there is not sufficient data at this time to support disease related claims for the population, including the elderly, it is important to encourage adequate consumption of zinc.

Comments were received from two national professional organizations of nutritionists and public health nutrition directors. These comments advised a cautious approach to the use of health claims on foods and supplements with awareness of the potential for abuse and misinterpretation of health claims. The comments recommended that the cornerstone for approval of a health claim be significant scientific agreement that the claim is supported by publicly available evidence, and that health claims be evaluated in the context of the total diet rather than on the basis of individual foods, supplementation, or fortification practices.

The Government of Canada submitted information that it considers helpful in the context of increased harmonization of regulations or standards affecting trade in specific products. The Canadian Food and Drugs Act prohibits advertising and labeling of a food as a treatment, preventative, or cure for specific diseases and disorders listed in the act. The Director General, Food Directorate, Health and Welfare Canada, stated that although immune function is not included in the act, health claims regarding zinc and immune function in the elderly would likely result in a food product being classified as a drug by virtue of the definition of "drug" embodied in the Canadian Food and Drugs Act.

The official position of Canada on the relationship of diet and nutrients to disease and the metabolic effects of nutrients is stated in "Nutrition Recommendations, the Report of the Scientific Review Committee—1990" (Ref. 27) (the Canadian Report). In sections relating to zinc and disease prevention, this report noted that abnormal zinc intakes have been associated with impaired immune function. Zinc supplementation of zinc-deficient persons improves many aspects of immune function. The report did not specifically address the issue of zinc and immune function in the elderly.

The Canadian report noted that excessive intakes of zinc have been shown to impair immune function and to cause adverse effects on copper metabolism (Ref. 27). In view of potential detrimental effects of high intakes of zinc on the immune system and on copper metabolism, the Canadian report suggested that large supplementary amounts of the element be avoided. There is no scientific evidence, the Canadian report continued, to support ingestion of megadoses of zinc except in the treatment of specific diseases such as Wilson's disease, in which excess copper is absorbed and stored in the body. The recommended zinc intakes for Canadian adult males and females (over 13 years of age) are 12 and 9 milligrams (mg) zinc per day, respectively (Ref. 27).

II. Review of the Scientific Evidence

A. Federal Government Documents

The Joint Nutrition Monitoring Evaluation Committee (JNMEC) DHHS/USDA, was established in 1983 by the USDA and DHHS to coordinate survey methods used by the two departments to obtain information on nutritional status of the U.S. population. The first report (Ref. 28), issued in 1986, provided food intakes data from the 1977 to 1978 Nationwide Food Consumption Survey (NFCS) and information on nutritional status based upon biochemical analyses from the National Health and Nutrition Examination Survey (NHANES II, 1976 to 1980). JNMEC judged that zinc was among a number of nutrients and dietary components that required further investigation because data regarding intake and nutritional status were inadequate (Ref. 28).

The "Surgeon General's Report on Nutrition and Health" (Ref. 22) did not consider the specific topic of zinc and immune function in the elderly. In sections dealing with infection and immunity and with aging, however, the Surgeon General's Report (Ref. 22) noted that deficiencies of a number of nutrients have been associated with reduced function of specific components of the immune system, and that during aging there is a gradual senescence of some components of the immune system. The Surgeon General's report pointed out, however, that distinguishing age related physiologic changes from those changes caused by poor nutrition in older persons has not yet been possible (Ref. 22). The Surgeon General's report observed that research has not yet resolved whether progressive impairment of cellular immunity with age might cause older populations to have more infections than young people of equivalent nutritional and health status. The relationships among malnutrition, infections, and changes in immune system function in elderly persons have yet to be clarified (Ref. 22).

The Surgeon General's Report (Ref. 22) further noted that nutritional status evaluation of older people is complicated, and that clinical and dietary standards for younger adults may not be appropriate for older persons. Few data are available on nutritional requirements of older adults. A very serious problem in nutritional status assessment of older adults is the lack of correlation between dietary intake data and clinical and laboratory assessment methods (Ref. 22).

B. Other Documents

The Food and Nutrition Board of the National Academy of Sciences did not specifically address the topic of zinc and immune function in the elderly in the Tenth Edition of "Recommended Dietary Allowances," (Ref. 25). The Food and Nutrition Board concluded that marginal states of zinc nutriture may exist in segments of the U.S. population, but that the data are fragmentary.

The Life Sciences Research Office report reviewed the literature on the relationship between zinc and immune function in the elderly (Ref. 26). This report concluded that:

(1) Zinc is of profound importance for proper immune system function. Too much or too little zinc can induce immunological dysfunctions. Steps to

return zinc nutriture to normal serve to correct such dysfunction;

(2) Elderly persons who are poor, who live alone or in institutions, who are female, who have acute or chronic illnesses or disabilities, or who reach very advanced ages are at risk for developing zinc malnutrition;

(3) Immunological dysfunctions in the elderly have been improved by nutritional means, but the role of zinc in this remains unclear. Reported immune system improvements induced by supplemental zinc generally occurred in subjects with preexisting evidence of zinc deficiency;

(4) RDA intakes of zinc may not correct preexisting zinc deficiencies in the elderly. Even large supplements may not improve plasma zinc values if disease induced zinc sequestering mechanisms are involved; and

(5) There is no definitive evidence to suggest that the current RDA for zinc is inadequate for healthy elderly individuals. Elderly persons who are truly zinc deficient may benefit immunologically from medically supervised nutritional rehabilitation.

C. Review of Scientific Literature

1. Evidence for an Association Between Zinc Intake and Immune Function in the Elderly

a. *Introduction.* FDA reviewed all the publicly available evidence on zinc and immune function in the elderly provided by intervention studies. The agency evaluated these human intervention studies to determine whether there is an association between zinc supplementation and improvements in immune function in this age group. Pertinent information regarding these studies, such as study design, number of subjects studied, nature and duration of supplement use, and significant results are included in Table 1. The evaluation focused on studies in which supplemental zinc was administered to healthy elderly persons to determine whether zinc had specific effects on the immune system function of the general population for which health claims are targeted.

TABLE 1.—ZINC AND IMMUNE FUNCTION IN THE ELDERLY: SUPPLEMENTATION STUDIES

Reference	Study design and duration	Description of subjects	Test material and intake level	Diet	Additional treatments	Other factors affecting interpretation	Results	Assessment of study
Duchateau et al., 1981 (Ref. 29)	Prospective intervention study with controls; 1 month.	30 healthy institutional patients, age >70 years; test group (n=15), control group (n=15); Belgium	Zinc (Zn) sulfate; 100 mg Zn/day orally.	Not reported.....	Tetanus vaccination.	Institutionalized subjects only. No measure of Zn status. No blinding	20% increase of T lymphocytes ($p<.05$), improved DCH response ($p<.01$), and greater post vaccine tetanus titre ($p<.001$) in treated group. No change of in vitro LPR.	Results not applicable to free-living elderly. Immunological improvement small, no assessment of initial Zn status
Wagner et al., 1983 (Ref. 30).	Prospective intervention study, not controlled; 1 month.	5 anergic, low income elderly, age 64 to 76 years; Alachua Co., FL.	Zinc sulfate; 55 mg Zn/day orally.	Self-selected.....	None	Incomplete serum data from 1 subject. Low income subjects only. All subjects initially anergic.	All 5 subjects had at least 1 positive DCH response from 5 test antigens. Serum Zn increase.	Small, uncontrolled, unblinded study.
Bogden et al., 1988 (Ref. 34).	Prospective double-blind intervention study; 3 months.	103 healthy free living elderly, age 60 to 89 years, 3 groups placebo (n=36), 15 mg Zn (n=36), 100 mg Zn (n=31); Bergen Co., NJ.	Zinc acetate, 15 mg Zn/day, 100 mg Zn/day, 0 mg Zn/day (lactose placebo) orally.	Self-selected 8 to 9 mg Zn/day.	Multiple vitamin-mineral (-Zn) oral supplement.	Free living healthy subjects. Compliance monitored by pill counts.	Plasma Zn increase ($p<.05$) in 100 mg Zn group Increase DCH response in all groups Decrease anergy same in all groups. No change of in vitro LPR.	Large, well conducted study, no differences were found in immune functions between placebo and Zn supplemented groups. No effect of supplemental Zn on immune function.
Bracker et al., 1988 (Ref. 35).	Prospective double-blind intervention study; 2 months.	41 healthy elderly, age 64 to 90 years, Zn supplemented group (n=23), placebo group (n=18); California.	Zinc gluconate; 0 mg Zn/day (placebo) 50 mg Zn/day orally.	Not reported.....	Trivalent influenza vaccine at 1 month	41 of 60 subjects (68%) completed study. Dietary assessment not included	45% increase in serum Zn in supplemented group ($p<.001$) Post vaccination antibody titre increase not different between supplement and placebo groups.	Limited to healthy subjects, results can be generalized to U.S. population. Previous influenza vaccination may have influenced results.
Soltesz et al., 1988 (Ref. 31)	Prospective intervention study; 4 weeks	6 nursing home residents, age not specified Ohio	Zinc gluconate, 15 mg Zn/day orally	Institutional food, 6.8 to 13 mg Zn/day calculated intake	One subject received liquid nutritional supplements	Nursing home patients, screened for confounding problems. Age not specified Data from 5 subjects.	Small increase in number of positive DCH responses ($p<.05$, $n=5$)	Small, uncontrolled, unblinded study, immunological improvement small
Cossack, 1989 (Ref. 32)	Prospective intervention study; 4.5 months.	8 Zn deficient, low income elderly men, age 65 to 78 years Denmark	Zinc acetate; 60 mg Zn/day orally	Not reported	None	Comparison values from 13 age matched men Subjects selected from group of low socioeconomic men on basis of low Zn status and anergy	Plasma and cellular Zn levels increase to normal DCH response and RBC[1] nucleoside phosphorylase activity increase to near normal.	Small, uncontrolled, unblinded study Results applicable only to individuals diagnosed as Zn deficient.

Bogden et al., 1990 (Ref. 34).	Prospective double-blind intervention study; 16 months overall, last 4 months all groups received placebo.	63 healthy free living elderly, age 60 to 389 years; 3 groups: placebo (n=24), 15 mg Zn (n=20), 100 mg Zn (n=19); Bergen Co., NJ.	Zinc acetate 15 mg Zn/day, 100 mg Zn/day, 0 mg Zn/day, (placebo) orally.	Self-selected: Zn intake less than 2/3 RDA for 67% of men and 81% of women.	Multiple vitamin-mineral (-Zn) oral supplement continued for 16 months.	Free living healthy subjects. 63 of 158 subjects (40%) completed 16 months. Zn supplementation for 12 months, all groups received placebo final 4 months. Compliance monitored by pill counts.	Plasma Zn increase ($p<.05$) in 100 mg Zn group, returned to baseline at 16 months. No change in cellular Zn except for transient increase of PMN[2] Zn at 3 months in 15 mg Zn group. DCH response increased in all groups, doubled in placebo group, increased least in Zn supplement groups DCH suppression in Zn groups persisted after Zn supplementation discontinued. Transient increase NK cell activity at 3 month in 100 mg Zn group.	Large, well conducted study. Improvements in immune function likely due to multivitaminminer supplement, and suppressed by supplemental Zn.
Soltesz et al., 1988 (Ref. 31).	Prospective intervention study; 4 weeks.	6 nursing home residents, age not specified. Ohio.	Zinc gluconate; 15 mg Zn/day orally.	Institutional food; 6.8 to 13 mg Zn/day calculated intake.	One subject received liquid nutritional supplements.	Nursing home patients, screened for confounding problems. Age not specified. Data from 5 subjects.	Small increase in number of positive DCH responses ($p<.05$, n=5).	Small, uncontrolled, unblinded study; immunological improvement small.
Cossack, 1989 (Ref. 32).	Prospective intervention study; 4.5 months.	8 Zn deficient, low income elderly men, age 65 to 78 years Denmark.	Zinc acetate; 60 mg Zn/day orally.	Not reported.....	None.....	Comparison values from 13 age matched men. Subjects selected from group of low socioeconomic men on basis of low Zn status and anergy.	Plasma and cellular Zn levels increase to normal DCH response and RBC nucleoside phosphorylase activity increased to near normal.	Small, uncontrolled, un blinded study. Results applicable only to individuals diagnosed as Zn deficient.

[1] Red blood cells.
[2] Polymorphonuclear cells.

FDA did not review studies of: (1) Influence of zinc on immune function in disease states; (2) effects of in vitro addition of zinc to lymphocytes; or (3) animal studies. The results of studies of immune function in malnourished populations and in specific disease states are widely reported in the scientific literature (Refs. 1 through 8, and 10). Such studies, however, do not contribute specific information helpful in evaluating the relationship of zinc to immune function in the elderly because it is difficult to identify the role of zinc versus other nutrient insufficiencies or to extrapolate from sick persons to the general population of healthy elderly in the United States. To the extent that zinc is used to cure, treat, or mitigate a disease, it is a drug (21 U.S.C. 321(g)(1)(B)).

The relevance of findings of effects of addition of zinc to lymphocytes in vitro to function of the immune system in vivo is simply not clear. Studies with animals have repeatedly demonstrated the effects of zinc deficiency on immune function. Thus, the existence of a role for zinc in immune function is not at issue. However, animal studies in general, while providing invaluable insights into the role of nutrition in immune function, do not contribute directly to an understanding of zinc and immune function in the elderly human population in the United States, the subject that the statute directs FDA to consider.

b. *Criteria used in evaluating evidence.* The criteria used in evaluating evidence included: (1) Reliability and accuracy of the methods used in food intake analysis and measurement of endpoints; (2) choice of control subjects (e.g., hospital-based versus population-based); (3) representativeness of subjects; (4) control of confounding factors in data analysis; and (5) degree of compliance and how compliance was assessed.

FDA evaluated the weaknesses and strengths of individual studies (see "Assessment" column of Table 1). The agency then assessed the strength of the overall combined evidence taking into account the strength of the association, the consistency of findings, and specificity of the association. FDA's conclusions reflect the strength, consistency, and preponderance of data.

c. *Review of evidence.* In 1981 Duchateau et al. (Ref. 29), published the first report of an effect of zinc supplementation on immunocompetence in healthy elderly persons. Two age and sex matched groups of institutionalized healthy persons over 70 years old were studied. One group (n=15, mean age=81) received 100 mg zinc per day orally for 1 month; the second group (n=15, mean age=80) received no supplement and served as a nonblinded control group. No measures of zinc status nor of dietary zinc intake were reported in the study. Several measures of cell-mediated immunity (proportion of T cell lymphocytes, DCH response, and antibody response to tetanus toxoid vaccination) increased in the zinc supplemented group but not in the control group. No differences between groups were noted for other indicators of immunocompetence, i.e., in vitro LPR to mitogens and numbers of circulating leukocytes or total lymphocytes. Side effects, including transient nausea and mild diarrhea, were noted in 5 of 15 zinc supplemented subjects (Ref. 29).

Another report associating zinc supplementation and improved immunocompetence in the elderly, as measured by DCH response, was reported in 1983 by Wagner et al. (Ref. 30). Five low income elderly (age 64 to 76 years) individuals in Alachua County, FL, who showed no DCH responses on two occasions before zinc supplementation, were supplemented with 55 mg zinc per day orally. Following one month of supplementation, all five subjects developed a positive DCH response to at least one of five test antigens. Serum zinc concentration increased in the four subjects for whom both initial and final serum samples were obtained. A control group was not included in this study, and only a single indicator of immunocompetence was measured (Ref. 30).

A study of six elderly nursing home patients (ages not stated) reported improved DCH following oral zinc supplementation (Ref. 31). Dietary zinc intake of the six subjects ranged from 6.8 to 13 mg per day. Subjects received oral zinc supplements of 15 mg zinc per day, as zinc gluconate, for 28 days. Plasma zinc and DCH responses were evaluated before and after the supplementation period. Serum zinc levels increased significantly with zinc supplementation (paired t-test, $p<.05$, $n=5$). Mean serum zinc, initially 98 micrograms per deciliter (μg per dL), increased to 102 μg per dL following zinc supplementation. Five of the subjects were tested for DCH responses to four test antigens. The number of positive responses increased significantly from a mean of 1.8 positive reactions per subject before zinc supplementation to 2.8 positive reactions per subject after zinc supplementation (paired t-test, $p<.05$, $n=5$). Nonsupplemented control subjects were not included. Of the six test subjects, one subject received liquid nutritional supplementation for weight gain, and one subject did not participate in DCH testing (Ref. 31).

In a study of immune function in zinc-deficient elderly subjects, Cossack (Ref. 32) selected eight zinc-deficient subjects from among 50 relatively healthy, low-socioeconomic status men age 65 to 78 years. Zinc deficiency was determined on the basis of "low status of zinc," subnormal DCH reactions, and low red blood cell (RBC) activity of a zinc-dependent enzyme (nucleoside phosphorylase) relative to normal values for healthy men of the same age. The zinc-deficient subjects received 60 mg zinc per day for 4.5 months, after which zinc concentration of plasma, RBC's, and white blood cells increased to normal values. The number of positive DCH responses to 4 test antigens increased from a mean of 2.1 positive responses per subject before supplementation to 3.1 positive responses per subject after supplementation. Zinc status and DCH reactions in the zinc-deficient subjects after zinc supplementation were comparable to the normal values determined for 13 healthy men of the same age (Ref. 32).

FDA believes that little weight can be given to these studies. The numbers of subjects in these four studies were quite small (eight or fewer subjects in three studies), providing little confidence in the results. Initial nutritional status of the institutionalized subjects, and reason for institutionalization, were not reported by Duchateau et al. (Ref. 29). Two of these studies (Refs. 30 and 32) were uncontrolled case reports on the effects of zinc supplementation of initially anergic or low zinc status elderly individuals selected from elderly populations surveyed for nutritional status and immunological indices. Similarly, the study of Soltesz et al. (Ref. 31) was uncontrolled and not blinded. Many potentially confounding factors in these studies were not considered or were not reported. Such factors include lack of dietary assessment, use of institutionalized elderly, and lack of monitoring for compliance with supplementation. Most importantly, the health significance, if any, of the findings of these studies with respect to enhanced resistance to disease is unknown.

Bracker et al. (Ref. 33) reported no effect of zinc supplementation on the antibody response to influenza vaccination. In this study, 41 healthy persons, age 64 to 90 years, were randomly assigned to supplemented (n=23; 50 mg oral zinc per day) or placebo (n=18) groups in a double-blind

2 month study. Subjects with diabetes, cancer, chronic renal disease, malabsorption, or senile dementia were excluded from the trial. Initial serum zinc was 80 ± 10 μg per dL, increasing to 116 μg per dL (mean value) in the supplemented group and 84 μg per dL (mean value) in the placebo group. Following the first month of supplementation, initial influenza antibody titres were measured, and trivalent influenza vaccine was administered. Influenza antibody titres were measured again following the second month of supplementation. No influence of zinc supplementation on post-vaccination increase of antibody titre was observed (Ref. 33).

Two recent well-controlled clinical studies by Bogden et al. (Refs. 34 and 35) failed to support the hypothesis that zinc supplementation can improve immunocompetence in the elderly. The first of these (Ref. 34) reports the findings of a double-blind, 3 month oral supplementation study of 103 apparently healthy, free-living persons, aged 60 to 89 years recruited from senior citizen centers in Bergen County, NJ. Subjects with a history of cancer, recent infectious disease, those on corticosteroid or estrogen therapy, or those using zinc supplements were excluded from the study. The subjects were randomly assigned to 3 groups: placebo (n=36), 15 mg zinc per day (n=36), and 100 mg zinc per day (n=31). All subjects received a daily multiple vitamin-mineral supplement without zinc in addition to oral zinc (or placebo) supplements. Compliance to supplementation was determined by a pill count at 3 months. A dietary questionnaire consisting of a food frequency checklist and a 24 hour dietary recall of the prior day's meals was also administered. The subjects consumed self-selected diets, providing an estimated average intake of 8 to 9 mg zinc per day. Plasma zinc increased from initial levels (84 to 86 μg per dL) in the group supplemented with 100 mg zinc per day but not in the placebo or 15 mg zinc per day groups. There were no changes from mean baseline zinc levels in RBC's, mononuclear cells, polymorphonuclear (PMN) cells, or platelets at 3 months in any group. There was a tendency for increased DCH responses after 3 months in all groups, and the increase was not different among groups.

Thirty study subjects, spread among the study groups, were initially anergic for DCH responses. The proportion of initially anergic subjects who developed positive DCH responses at 3 months was not different between placebo and zinc groups. In addition, there was no effect of zinc supplementation on in vitro LPR. In this study neither the cellular immunity nor zinc status, as indicated by cellular zinc content, of healthy elderly individuals with usual dietary zinc intakes of approximately 66 percent of the RDA, was enhanced by zinc supplementation (Ref. 34).

The second study (Ref. 35) followed the same double-blinded three group study design, with supplements provided for 12 months, after which all groups were switched to the placebo for an additional 4 months. Of 158 individuals initially enrolled, 63 subjects completed the entire 16-month study period, giving a response rate of 40 percent. The placebo group consisted of 24 persons. Twenty persons were included in the 15 mg zinc per day-supplemented group, and 19 persons were included in the 100 mg zinc per day-supplemented group. Dietary zinc intake (mean of 8.6 mg per day for males and 7.8 mg per day for females) from self-selected diets was similar among the three treatment groups and consistent over the course of the trial. Plasma zinc (initially about 85 μg per dL) increased only in the group taking 100 mg zinc per day and returned to baseline after zinc supplementation was discontinued. Monocyte, polymorphonuclear, erythrocyte, and platelet zinc levels were not altered, except for a transient increase of polymorphonuclear zinc in the 15 mg zinc per day group which returned to baseline at 12 months. DCH responses in all groups increased continuously over the study to about twice the initial values. The increase in DCH response was significantly greater in the placebo group than in either zinc-supplemented group. Furthermore, the suppression of the increased DCH response in the zinc-supplemented groups persisted 4 months after zinc supplementation was discontinued. The in vitro LPR increased during the study, particularly in the placebo group. There was a transient increase of T lymphocyte killer cell activity in the 100 mg zinc per day group, which did not persist beyond 3 months.

The authors speculate that the progressive increase of DCH response may be the result of a booster effect of repeated skin tests or a response to the multiple vitamin/mineral supplement administered to all subjects or to other unknown factors (Ref. 35). Except for a transient increase of natural killer cell function, this study did not show that zinc supplementation improved cellular immunity in the elderly. In fact, zinc at both doses appeared to have retarded improvement of cellular immunity. Lack of increased cellular (monocyte, polymorphonucleocyte, erythrocyte, and platelet) zinc levels with zinc supplementation suggests that the population was not zinc deficient, even though average dietary zinc intake was apparently well below the RDA (Ref. 35).

2. Other Relevant Information

a. *Physiological changes in aging.* Physiological changes of aging have effects on normal zinc metabolism and homeostasis, particularly the efficiency of intestinal absorption of zinc (Ref. 36). Average zinc absorption in six men aged 65 to 74 years and in six men aged 22 to 33 years was 17 percent and 31 percent, respectively (Ref. 36). This difference in zinc absorption between elderly and young men was significant. However, endogenous zinc losses in the elderly men were proportionally less than those in the younger men. There was no difference between young and elderly men in zinc balance. Lower zinc absorption in elderly men may reflect a lower requirement for zinc in the elderly. Homeostatic mechanisms also strongly influence zinc absorption. With decreasing zinc intake, the efficiency of intestinal zinc absorption increases, and excretion of endogenous zinc decreases. Thus the body is capable of adapting to variations in dietary zinc intake through increasing absorption and reducing endogenous loss (Ref. 36).

b. *Zinc status in the elderly.* The adult RDA (Ref. 25) for zinc is 15 mg per day for men and 12 mg per day for women. Differences in values for men and women reflect sex-related differences in body weight. The RDA is not a requirement below which deficiency diseases are apt to develop. Rather, for many nutrients, they are set at sufficiently high levels to cover the needs of practically all healthy individuals. Because individuals differ in their requirements for specific nutrients, it is impossible to know from a dietary survey which person requires at least the RDA and which one requires less or, in rare cases, possibly more. The intent of the RDA is to provide the basis for recommendations for healthy diets and for planning for the national food supply to improve the nutritional status of the population. It is not an appropriate use of the RDA to assert that adherence to the RDA will ensure protection against disease, or that intakes less than the RDA are necessarily inadequate or deficient (Ref. 25).

Dietary intake data are available from large national surveys such as the NFCS

conducted by the USDA and the NHANES II conducted by the National Center for Health Statistics (NCHS) (Ref. 37). NHANES III, which is currently in progress (1988 to 1994), will be the first NHANES to include sampling of the population older than 74 years of age. Other current data on nutritional status of older Americans comes from cross-sectional studies on relatively small selected samples.

Using the 1977 to 1978 NFCS and 1976 to 1980 NHANES II food consumption data bases, FDA's Total Diet Study designed diets to be representative of food intakes of men and women aged 60 to 65 years. Chemical analysis of the zinc content of these representative diets provided estimated average zinc intakes of 73 percent and 86 percent of the RDA for women and men, respectively, aged 60 to 65 years (Ref. 38). In smaller studies, dietary zinc intakes of institutionalized or house bound elderly people tended to be lower than those of free-living elderly persons (Refs. 16 and 17).

A recent review of studies of zinc intake by elderly individuals (Ref. 14) showed consistent average intake of 7 to 11 mg zinc per day. Two prospective zinc intervention studies of elderly subjects (Refs. 35 and 39) reported average dietary zinc intake of 8 to 9 mg per day which is consistent with other reports (Refs. 14 and 38).

It seems likely, from such studies, that some of the elderly in the United States consume less than the RDA for zinc. However, this finding does not necessarily imply that these elderly persons are consuming inadequate amounts of zinc. There is increasing evidence that these types of food intake estimates may underestimate food and nutrient intakes by significant amounts (Ref. 40). A more complete evaluation of problems of sensitivity and specificity of nutrient intake based on dietary recall data and the difficulty in predicting nutritional status from dietary data alone were described in a National Academy of Science report (Ref. 41).

Dietary data frequently estimate nutrients from foods alone. Contributions of dietary supplements are rarely considered but can provide significant quantities of zinc to total daily intake. The 1986 National Health Interview Survey showed that 38 percent of elderly Americans consumed over-the-counter vitamin and mineral products at least once during a 2-week period, with a median zinc intake of 100 percent of the RDA (Ref. 42). Another survey of elderly persons in the Boston area, found regular multivitamin-mineral use in 31 percent of males and 43 percent of females which supplied an average of 10 mg of zinc per day (males) and 9 mg zinc per day (females) (Ref. 43).

The best measures for determining nutritional status of human subjects are clinical and biochemical measures. Data on the nutritional status of the U.S. population have been collected in the NHANES. Results from NHANES II (1976 to 1980) were used to evaluate the prevalence of low serum zinc levels (defined as serum zinc less than 70 μg per dL for morning fasting blood samples) in the U.S. population (Ref. 44). The prevalence of low serum zinc levels was 3 percent in both males and females among the elderly (age 65 to 74 years). The prevalence across all ages was 1.3 percent for males, and an overall adjusted prevalence (excluding oral contraceptive users, pregnant, recently pregnant, and lactating women) of 2.1 percent was observed for females. Serum zinc reached peak levels in young adulthood (93 μg per dL in males; 85 μg per dL in females) and declined with age. Mean serum zinc levels for the elderly age group (65 to 74 years) were well within normal range (86 and 84 μg per dL for males and females, respectively). Poverty status was not associated with serum zinc levels in the elderly age group. Overall, blacks tended to have lower serum zinc values than did whites; however, there was no racial difference in serum zinc levels within the elderly age group (Ref. 44). Two prospective zinc intervention studies of elderly subjects (Refs. 35 and 39) also found mean serum zinc levels (about 86 μg per dL) to be within the normal range and consistent with NHANES data (Ref. 44).

An expert panel was convened to evaluate the usefulness of the serum zinc values from the NHANES II in determining the zinc nutritional status of the U.S. population (Ref. 44). This panel concluded that serum zinc values by themselves are not definitive for the assessment of zinc nutritional status because many factors besides zinc deficiency can depress serum zinc levels, e.g., stress/inflammatory response, albumin levels, diurnal variations, and meal consumption/fasting effects. In these cases, increasing zinc intake would not likely be effective in improving zinc status.

A recent report of the ad hoc Expert Panel on National Nutrition Monitoring, which reviewed data available through the National Nutrition Monitoring System of the USDA and DHHS, concluded that zinc is not a current public health issue to be assigned high priority, but that it does constitute a potential public health issue for which further study is needed (Ref. 45). The report also noted the discrepancy between apparently high percentages of people with moderate to low dietary intake and very small percentages of persons with low serum values. The Expert Panel on National Nutrition Monitoring recommendation for further research was made in recognition of the fact that the significance of the observed low dietary intakes of zinc cannot be evaluated without additional research to determine zinc requirements and to develop better measures of zinc status.

Zinc nutritional status is difficult to assess because of the lack of reliable noninvasive and specific methods and of the confounding of available measures of zinc status by factors unrelated to zinc insufficiencies. Thus the prevalence of poor zinc nutrition in the U.S. elderly is unknown. While zinc levels of blood cellular components has been proposed as a criterion for diagnosing mild zinc deficiency (Ref. 46), values for the general healthy elderly population in the United States are not currently available (Ref. 47). The high percentage (97 percent) of serum zinc values in the normal range for 65 to 74 year age group in the NHANES II do not provide compelling evidence of inadequate zinc nutriture in this population.

c. *Safety considerations.* The National Academy of Sciences in "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 24) and "Recommended Dietary Allowances" (Ref. 25) discussed potential health risks associated with oral zinc supplements. Considering the potential risks, these reports recommended against chronic ingestion of zinc supplements exceeding 15 mg per day (Refs. 24 and 25). Oral zinc supplementation at higher levels (e.g., 100 mg of zinc per day) is reported to suppress immune function (Ref. 48). Oral supplementation of 300 mg zinc per day was administered to 11 healthy males for 6 weeks. Subjects consumed self-selected diets providing an average of 11 mg per day. At 4 and 6 weeks several measures of immunocompetence were decreased (e.g., LPR and polymorphonuclear chemotaxis and phagocytosis). Other measures of immunocompetence (e.g., total number of lymphocytes, T cells, and B cells) were not altered during zinc supplementation. Duchateau et al. (Ref. 49), reported that zinc supplementation with 150 mg day for one month had a normalizing effect on LPR, increasing the response in individuals with initial low response but inhibiting LPR in individuals with initial values above the average.

Zinc intake in the range of 100 to 300 mg per day is reported to induce copper deficiency with attendant anemia, impaired immune function, and adverse effects on the low density lipoprotein/high density lipoprotein (LDL/HDL) cholesterol ratio (Ref. 25). There is also evidence that use of zinc supplements at lower levels (15 to 100 mg per day) may have adverse effects on copper balance and HDL-cholesterol which are similar to the problems of higher zinc doses (Refs. 9 and 50). Supplemental zinc ingestion, even at levels close to the RDA, appears to block the effect of exercise on raising serum HDL-cholesterol in elderly individuals (Ref. 51). The effect of zinc intake on lowering HDL-cholesterol has been confirmed in other reports (Refs. 48 and 52).

3. Conclusions

There are publicly available data for seven human studies in which elderly subjects were supplemented with zinc to determine the influence on immune system function. The earliest published study (Ref. 29) suggested a zinc-associated enhancement of several measures of immune function. Three additional studies in which a measure of cell-mediated immunity showed improvement with zinc supplementation selected initially anergic or zinc deficient subjects (Refs. 30 through 32). The results of the later studies are not relevant because they involved very few individuals, and the tested subjects were not representative of the general elderly population. The results discussed in these initial reports have not been substantiated by more recent, larger studies of more rigorous experimental design (Refs. 34 and 35). The later, larger studies showed no improvement of immunocompetence from zinc supplementation in the elderly. Furthermore, zinc supplementation at levels in excess of 100 mg per day can result in suppression of immune system function (Ref. 48). Thus, the publicly available data on the role of zinc in immune system function do not provide a sufficient scientific basis from which to conclude that immune function in the general elderly U.S. population can be improved by zinc supplementation.

Several comments requested that the agency also consider whether claims relating intakes of zinc by other age groups to improved immune function would meet the standard set forth in the 1990 amendments. Because of time and resource constraints, the agency did not broaden the scope of its considerations to include other age groups or nutrients. The 1990 amendments clearly identified zinc and immune function in the elderly as one of 10 specific topic areas for which the agency was to determine the validity of health claims.

In summary, proper dietary zinc levels are essential for adequate functioning of the immune system. Dietary zinc intake, serum zinc, and cell-mediated immunity all decline with advancing age. However, the available data do not provide a basis on which to conclude that increased zinc intake can reverse the age-related decline in immunocompetence in the general healthy elderly population in the United States. In fact, it may suppress immune function.

III. Tentative Decision to Deny a Health Claim Relating Zinc and Immune Function in the Elderly

The agency reviewed the publicly available scientific data and recent consensus documents on the association between the ingestion of zinc-containing supplements and immune system function in the elderly. The agency finds that the evidence provides no basis upon which to permit a health claim.

In 1988, the Surgeon General's report (Ref. 22) concluded that the available evidence was insufficient to determine if any age-related losses in immune function were caused by nutritional deficiencies. The human evidence that has become publicly available since the publication of that document does not provide adequate data to support a health claim relating the ingestion of zinc to improved immune system function in the elderly. Furthermore, the National Academy of Sciences publications, "Diet and Health" (Ref. 24) and "Recommended Dietary Allowances" (Ref. 25), raised safety concerns associated with oral zinc supplements. Finally, claims that zinc would prevent or treat any disease or health condition in the elderly would be a drug claim (FDA Health Fraud Bulletin No. 11, August 17, 1987).

The standard that FDA is proposing, in a companion document published elsewhere in this issue of the **Federal Register**, to apply to all foods is that there be significant scientific agreement that any health claim is supported by the publicly available evidence. For the topic of zinc and immune function in the elderly, the weight of the evidence is insufficient to support the claim, and there is no basis for scientific agreement that this claim is supported by the available evidence. Thus, the agency is proposing to add § 101.71(e) to deny the use on food, including dietary supplements, of health claims relating to an association between zinc supplementation and immune function in the elderly.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Effective Date

FDA is proposing to make these regulations effective 6 months after the publication of a final rule based on this proposal.

VI. Comments

Interested persons may, on or before February 25, 1992, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VII. Economic Impact

The food labeling reform initiative, taken as a whole, will have associated costs in excess of the $100 million threshold that defines a major rule. Therefore, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA has developed one comprehensive regulatory impact analysis (RIA) that presents the costs and benefits of all of the food labeling provisions taken together. The RIA is published elsewhere in this issue of the **Federal Register**. The agency requests comments on the RIA.

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 is revised to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371).

2. Section 101.71 is amended by adding new paragraph (e) to read as follows:

§ 101.71 Health claims: claims not authorized.

* * * * *

(e) Zinc and immune function in the elderly (insert cite and date of publication in the **Federal Register** of the final rule).

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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21 CFR Part 101

[Docket No. 91N-0103]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements: Omega-3 Fatty Acids and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing not to authorize the use on foods, including dietary supplements, of health claims relating to the association between omega-3 fatty acids and coronary heart disease (CHD). FDA has reviewed the scientific data on this topic and has tentatively concluded this evidence does not provide a basis upon which to authorize such a health claim. Examination of the epidemiological research on this topic revealed that the available studies applied only to the consumption of fish, which contain omega-3 fatty acids, and that it was not possible to ascribe any effects specifically to the omega-3 fatty acids. Examination of data from clinical studies revealed that the effects on blood lipids of fish oils containing omega-3 fatty acids were primarily a reduction of blood triglycerides, a blood lipid variable not considered to be an independent risk factor for CHD, but they had no effect on serum cholesterol, low-density lipoprotein (LDL) cholesterol, or high-density lipoprotein (HDL) cholesterol, the blood lipid variables most closely associated with risk of CHD. The scientific data are ambiguous on the effects of omega-3 fatty acids on blood pressure and other risk factors for CHD. Finally, the scientific data reveal unresolved safety issues: the potential for omega-3 fatty acids to increase LDL cholesterol of hyperlipidemics and to worsen control of blood glucose in diabetics.

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the Nutrition Labeling and Education Act of 1990.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John C. Wallingford, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-245-0835.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (Pub. L. 101-535) (the 1990 amendments), which amends the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and Human Services (the Secretary), and by delegation, FDA, to issue regulations authorizing nutrient content and health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under section 403(r) (1) (B) of the act (21 U.S.C. 343(r) (1) (B)).

Published elsewhere in this issue of the **Federal Register** is a proposed rule to establish general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs, and other nutritional substances (referred to generally as "substances") to a disease or health-related condition on food labels and in labeling. In this companion document, FDA has tentatively concluded that such claims would only be justified for substances in dietary supplements as well as in conventional foods if it determines, based on its review of the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (section 3(b)(1)(A)(ii), (b)(1)(A)(iv), and (b)(1)(a)(x)) that within 12 months of enactment, the Secretary shall issue